## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/2009 has been entered.

### *Status of the Claims*

1. The amendments filed 9/23/2009 were entered.

### *Response to Arguments*

2. Applicants' arguments, filed 9/23/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

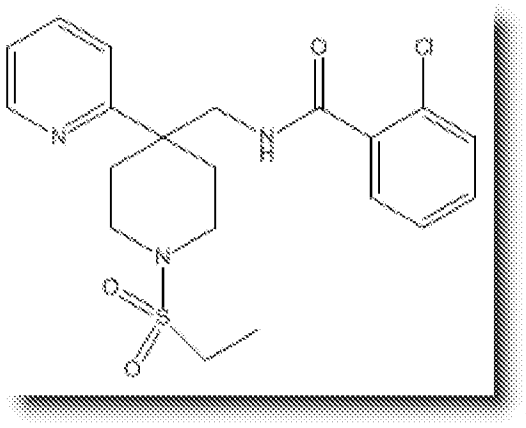
3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

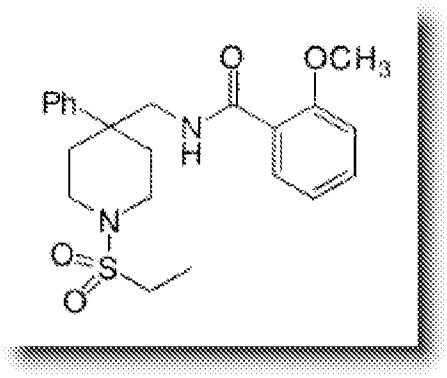
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 1-4, 10-14, 18-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bao et al* (cited in a previous Action) in view of *Williams et al* (cited in a previous Action) and *Patani et al* (cited in a previous Action)**.

6. As discussed in the previous Action mailed on 7/07/2009 and reiterated in large part herein, instant claim 1 is drawn to a compound of formula (I) which encompasses the following compound species  wherein $R^1$ is hydrogen; $R^2$ is phenyl, which is substituted with $R^{2a}$ and $R^{2a}$ is halogen; $R^3$ is $CH_2$-$CH_3$; $R^4$, $R^5$ and $R^6$ are hydrogen; W, X, Y and Z are C; and m is zero, which reads on claims 1-4, 11-14 and 18-19.

7. *Bao et al* teach the following compound  (Page 61, Example 18). Accordingly, *Bao et al* teach a structurally related compound which differs from the instant compound in two ways: FIRST, the phenyl in Example 18 (taught by *Bao et al*) is substituted with -$OCH_3$ whereas the phenyl in the instant compound is substituted with chloro; and SECOND, the other phenyl in Example 18 (taught by *Bao et al*) is pyridine in the instant compound. **Both** of the modifications to the compound taught by Example 18 in *Bao et al* would have been *prima facie* obvious for the following reasons:

8. As taught by *Williams et al* "[w]hen a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate… The medicinal chemist therefore must modify the compound to reduce or eliminate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as isosteric or bioisosteric replacement" (Page 59). Although it is clear that "the use of bioisosteric replacement (classical or nonclassical) in drug development is highly dependent upon the biological system being investigated" and that "[n]o hard and fast rules exist to determine what bioisosteric replacement is going to work with a given molecule" it is also clear that "some generalizations have been possible" (Page 60). Notably, as taught by *Patani et*

*al*, one such generalization is that -$OCH_3$ and -Cl can replace each other (Page 3154, Figure 18), a modification that was associated with a decrease in compound half-life. Furthermore, as taught by *Williams et al*, another such generalization is that -CH= and –N= (which are classic biosteric groups) can replace each other (Page 61, Table 2.9). Indeed, *Patani et al* similarly teach that benzene and pyridine are classic ring equivalent bioisosteres (Page 3158, Column 1). Accordingly, in view of *Williams et al* and *Patani et al* it would have been *prima facie* obvious to modify the compound taught by *Bao et al* (Example 18) by replacing the methoxy group with a chloro group. Specifically, the skilled artisan would have been motivated to replace -$OCH_3$ with -Cl in order to optimize the pharmacokinetic properties of the compound in view of *Williams et al* and *Patani et al* with a reasonable expectation of success. Additionally, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to replace the –CH= group in benzene (as taught by *Bao et al*) with –NH= to form pyridine (as recited by the instant claims). The person of ordinary skill in the art at the time the invention was made would have been motivated to make the bioisosteric modification to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior. Accordingly, instant claims 1-4, 10-14 and 18-19 are rejected as *prima facie* obvious.

9. Instant claim 23 is drawn to a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of claim 1 or salt thereof. *Bao et al* specifically disclose that "[a]lso within the scope of this invention are pharmaceutical formulations comprising a compound of Formula I and a pharmaceutical carrier" (Page 9, Lines 13-15). Accordingly, claim 23 is rejected as *prima facie* obvious.

10. Applicants, in arguments filed on 3/23/2009, traversed the rejection of claims on a variety of grounds. However, Applicants' arguments were not considered persuasive as discussed in the previous Action. That discussion is reiterated as follows:

11. **First**, on the grounds that "there is no indication from *Bao et al* that Example 18, as opposed to the other examples, would clearly be the starting reference point from which a skilled artisan might identify a problem and pursue potential solutions" (Applicant Argument, Page 16). As stated in MPEP 2144.08 "a genus may be so small that, when considered in light of the totality of circumstances, it would anticipate the claimed species or subgenus." Significantly, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would… envisage *each member*" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962, emphasis in original). Thus it is significant that *Bao et al* disclose only 20 examples. Accordingly, in the instant case, the skilled artisan would have been able to immediately envisage modifying any one of the 20 compounds (including Example 18) embodied by *Bao et al* according to *Williams et al* and *Patani et al*. As such, Applicants' argument is not found persuasive.

12. **Second**, on the grounds that *Williams et al* and *Patani et al* - which are general medicinal chemistry texts - do not disclose compounds (such as the instant compounds) having activity as GlyT or potassium channel inhibitors. As such, Applicants contend that "[o]ne skilled in the art with knowledge of *Bao* would in no way be looking to *Williams* [or Patani] for specific teachings to modify compounds active against these targets" (Applicant Argument, Page 17). Applicants' argument is not found persuasive. Although Applicant is correct that neither *Williams et al* nor

*Patani et al* are directed to GlyT or potassium channel inhibitors specifically, the skilled artisan would understand that *Williams et al* and *Patani et al* teach bioisosteric modifications which are applicable to compounds in general and which have been shown to predictably result in compounds having similar biological activity relative to the parent compound but distinct pharmacokinetic profiles. Since the compounds taught by *Bao et al* are "potassium channel inhibitors" (Title), the skilled artisan would have predicted that the well known bioisosteric modifications taught by *Williams et al* and *Patani et al* – when applied to the potassium channel inhibitors taught by *Bao et al* – would provide compounds having similar activity as potassium channel inhibitors, but with distinct pharmacokinetic profiles. Thus, the skilled artisan would have made the above discussed modifications in order to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior.

13. **Third**, via Declaration, Scott Wolkenberg identifies seven compound species, some of which demonstrate time dependent inhibition of CYP and some of which do not. Significantly, nothing is concluded by Mr. Wolkenberg in the Declaration. However, based on the Declaration, Applicants argue that "three out of the four 4-phenylpiperidine compounds were TDI+ while three out of three 4-pyridylpiperdine [sic] compounds were TDI-. This result clearly demonstrates an unexpected superior preclinical profile for the 4-pyridylpiperidine series over the 4-phenylpiperidine series" (Applicant Argument, Pages 17-18). However, this argument is not found persuasive since, in each instance, multiple modifications were made to the compared compounds. Thus, it is unclear whether the observed differences in activity were due to the

replacement of phenyl with pyridine, as asserted by Applicants, or due to the other modifications.

14. And **fourth**, Applicants also assert that "all the examples described in *Bao* have a methoxy group substituted on the benzamide portion, thus teaching away from the claims as presently amended" (Applicant Argument, Page 17). However, a disclosure that "does not criticize, discredit, or otherwise discourage the solution claimed" does not constitute a teaching away. *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004). As such, it is not found persuasive that *Bao et al* teach away from the well known bioisosteres $-OCH_3$ and -Cl.

15. Applicants, in arguments filed on 9/23/2009, continue to traverse the obviousness rejection. In particular, Applicants argue that it would not have been obvious to replace $-OCH_3$ with -Cl in order to optimize the pharmacokinetic properties of the compound taught by *Boa et al* in view of *Williams et al* and *Patani et al* **with a reasonable expectation of success**. Specifically, referring to *Lindsley et al*, Applicants argue that the evidence demonstrates the high unpredictability of the art, with small changes in structure having a large impact on activity. Indeed, *Lindsley et al* evaluated the effect of replacing the methoxy group in a potassium channel inhibitor which is nearly identical in structure to the compound taught by *Bao et al* and found that "the 2-OMe benzamide moiety was the key to the... potassium channel activity, as... 2-halogen substituted analogues... possessed no potassium channel activity" (Page 808, Column 1). Thus, Applicants argue that the skilled artisan would not have replaced $-OCH_3$ (which is present in each of the embodiments of *Bao et al*) with -Cl with a reasonable expectation of retaining potassium channel activity (Applicant Argument, Page 2). Although Applicants are correct, it is significant that the *Lindsley et al* document was published in August of 2006. Thus, the skilled

artisan, ***at the time the invention was made***, would not have been aware of the *Lindsley et al* document. Rather, the skilled artisan would have relied on teachings at the time, such as, for example, *Patani et al*, which demonstrate replacement of $-OCH_3$ with -Cl provides compounds having similar activity and would have reasonably predicted that applying the same modification to the compound taught by *Bao et al* would similarly provide a compound having similar activity. Accordingly, Applicants' arguments are not found persuasive.

16. **The rejection of claims is maintained**.

17. However, the finding that the instant compounds are GlyT1 inhibitors which ***lack*** potassium channel activity could possibly be considered **unexpected results** since the skilled artisan (at the time the invention was made) would have predicted that the modification to the compound taught by *Bao et al* would result in compounds which ***retain*** potassium channel activity. Although Applicants have not asserted unexpected results, evidence of unexpected results can be used to overcome a rejection under 35 U.S.C. 103(a). However, Applicants are reminded that the claims must be drafted commensurate in scope with the unexpected results in order to overcome the rejection. The claims, as currently presented, are not so limited.

***Double Patenting***

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

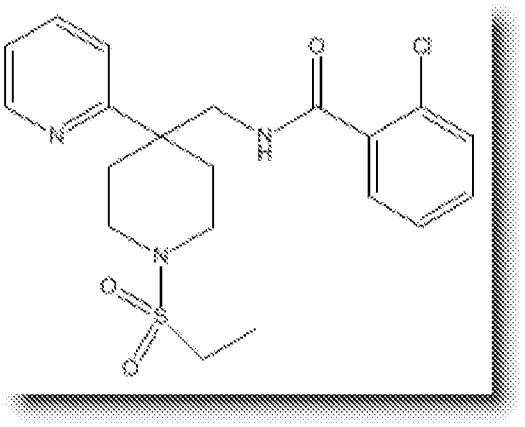
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. **Claims 1-8, 10-14, 18-19 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4 and 18 of copending Application No. 10/579,261 in view of *Williams et al* (cited in a previous Action) and *Patani et al* (cited in a previous Action)**.

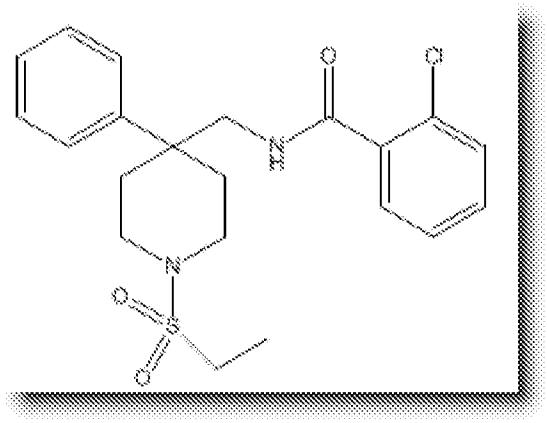
This is a provisional obviousness-type double patenting rejection.

20. As discussed above, instant claim 1 is drawn to a compound of formula (I) which encompasses the following hypothetical compound



wherein $R^1$ is hydrogen; $R^2$ is phenyl, which is substituted with $R^{2a}$ and $R^{2a}$ is halogen; $R^3$ is $CH_2$-$CH_3$; $R^4$, $R^5$ and $R^6$ are hydrogen; W, X, Y and Z are C; and m is zero, and which reads on claims 1-4, 10-14 and 18-19.

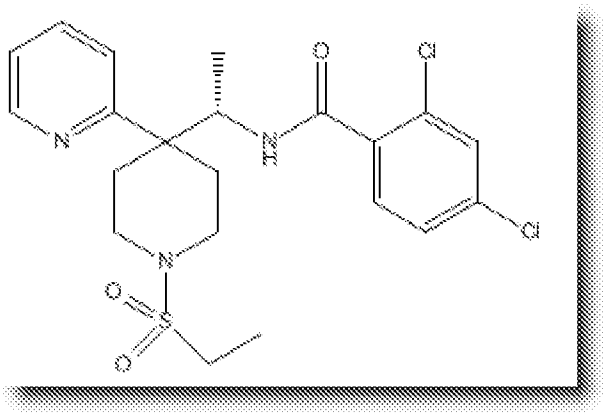
21. Claim 1 of the '261 application is drawn to a compound of formula (I) which encompasses the following hypothetical compound



wherein $R^1$ is hydrogen; $R^2$ is phenyl, which is substituted with halogen; $R^3$ is $CH_2$-$CH_3$; and $R^4$ and $R^5$ are hydrogen. Accordingly, the '261 application teaches structurally and functionally related compounds differing only in the substitution of benzene (as taught by the '261 application) with pyridine as recited by the instant claims.

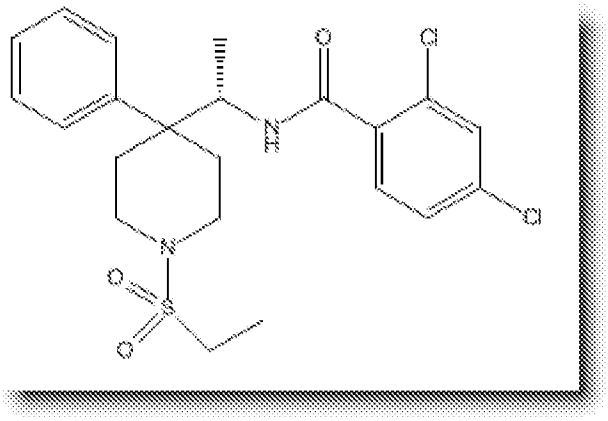
22. As discussed above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to replace benzene in the compounds taught the '261 application with pyridine as claimed in the instant application in view of *Williams et al* and *Patani et al*. The person of ordinary skill in the art at the time the invention was made would have been motivated to make the obvious bioisosteric modifications to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior.

23. Instant claim 1 also encompasses Applicant's elected specie; namely



which reads on claims 1-8, 11-14, 18-19 and 22.

24. Claim 4 of the '261 application is drawn to a compound of formula (Ib) which encompasses the following hypothetical compound



wherein $R^2$ is phenyl, which is substituted with one or more halogens; and $R^3$ is $CH_2$-$CH_3$. Notably, the only difference between the instant elected compound specie and the above compound encompassed by claim 4 of the '261 application is the substitution of benzene (as taught by the '261 application) with pyridine as recited by the instant claims. Accordingly, for all of the reasons discussed above, claims 1-8, 11-14, 18-19 and 22 (which are drawn to the instantly elected compound specie) are rejected.

25. Instant claim 23 is drawn to a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of claim 1 or salt thereof. Claim 18 of the '261 application recites a pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628

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